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מאי 2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא ובעלון לצרכן של התכשיר:

Stelara Prefilled syringe 1468133291
Stelara 45mg vial 1423632021
Solution for injection
Ustekinumab 45mg/0.5ml

המאושרים להתוויות הבאות:

Plaque psoriasis
STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adult patients (18 years or older) who have failed to, have a contraindication to, or who are intolerant to other systemic therapies including ciclosporin, methotrexate or Psoralen plus U.V (PUVA).

Paediatric plaque psoriasis
STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Psoriatic arthritis (PsA)
STELARA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

Crohn's Disease
STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

תוספת התוויה:

Ulcerative colitis
STELARA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.

השינויים המהותיים בעלון לרופא מופיעים בסעיפים הבאים:

4.2 Posology and method of administration

Crohn's Disease and Ulcerative Colitis
In the treatment regimen, the first dose of STELARA is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion SmPC.

The first subcutaneous administration of 90 mg STELARA should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may

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receive a second subcutaneous dose at this time (see section 5.1).

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see section 5.1, section 5.2).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see section 5.1).

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit ~~by week~~ 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose.

Immunomodulators and/or corticosteroids may be continued during treatment with STELARA. In patients who have responded to treatment with STELARA, corticosteroids may be reduced or discontinued in accordance with standard of care.

In Crohn's disease, ~~If~~ if therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).
In Ulcerative Colitis -The number of patients aged 65 and over is not sufficient to determine whether they response differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly

Renal and hepatic impairment
STELARA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of STELARA in treatment of Crohn's disease or ulcerative colitis in children less than 18 years have not yet been established. No data are available.

4.4 Special warnings and precautions for use

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Respiratory
Cases of allergic alveolitis, ~~and~~ eosinophilic pneumonia, and non-infectious organising pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment (see section 4.8).

….
Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5).
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Special populations
Elderly (≥ 65 years)
No overall differences in efficacy or safety in patients age 65 and older who received STELARA were observed compared to younger patients in clinical studies in approved indications, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with STELARA (see section 4.4).

No interaction studies have been performed in humans. In the population pharmacokinetic analyses of the phase ~~III~~ 3 studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids in patients with psoriatic arthritis, Crohn's disease or ulcerative colitis, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The results of an *in vitro* study do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see section 5.2).

In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. (see section 4.4).
…

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions (> 5%) in controlled periods of the adult psoriasis, psoriatic arthritis, ~~and~~ Crohn's disease and ulcerative colitis clinical studies with ustekinumab were nasopharyngitis and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for STELARA is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, ~~and~~ Crohn's disease and ulcerative colitis. ~~No new safety concerns were identified with up to 2 years of treatment in patients with Crohn's Disease.~~

Tabulated list of adverse reactions
The safety data described below reflect exposure in adults to ustekinumab in ~~12~~ 14 phase 2 and phase 3 studies in ~~5,884~~6,709 patients (4,135 with psoriasis and/or psoriatic arthritis, ~~and~~ 1,749 with Crohn's disease and 825 patients with ulcerative colitis). This includes exposure to STELARA in the controlled and non-controlled periods of the clinical studies for at least 6 months or 1 year (~~4,105~~4,577 and ~~2,846~~3,253 patients respectively with psoriasis, psoriatic arthritis, ~~or~~ Crohn's disease or ulcerative colitis) and exposure for at least 4 or 5 years (1,482 and 838 patients with psoriasis respectively).

Table 3 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, ~~and~~ Crohn's disease and ulcerative colitis clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by System Organ Class and frequency, using the

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following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 List of adverse reactions

System Organ Class	**Frequency: Adverse reaction**
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

* See section 4.4, Systemic and respiratory hypersensitivity reactions.

Description of selected adverse reactions

Infections

In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, ~~and~~ Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical studies ~~of patients with psoriasis, patients with psoriatic arthritis and patients with Crohn's disease~~, the rate of infection was 1.~~38~~ 36 per patient-year of follow-up in ustekinumab-treated patients, and 1.~~35~~ 34 in placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (~~27~~ 30 serious infections in ~~829~~ 930 patient-years of follow-up) and 0.03 in placebo-treated patients (~~11~~ 15 serious infections in ~~385~~ 434 patient-years of follow-up) (see section 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, ~~and~~ Crohn's disease and ulcerative colitis clinical studies, representing ~~10,953~~11,581 patient-years of exposure in ~~5,884~~6,709 patients, the median follow up was ~~0.99~~1.0 years; ~~3.2~~1.1 years for ~~psoriasis~~ psoriatic disease studies, ~~1.0 year for psoriatic arthritis studies and~~ 0.6 year for Crohn's disease studies, and 1.0 years for ulcerative colitis studies. The rate of infection was 0.91 per patient-year of follow-up in

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ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (~~178~~ 199 serious infections in ~~10,953~~11,581 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, ~~pneumonia,~~ diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancies
In the placebo-controlled period of the psoriasis, psoriatic arthritis, ~~and~~ Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.~~12~~ 11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in ~~829~~ 929 patient-years of follow-up) compared with 0.~~26~~ 23 for placebo-treated patients (1 patient in ~~385~~ 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.~~48~~ 43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in ~~829~~ 929 patient-years of follow-up) compared to 0.~~52~~ 46 for placebo-treated patients (2 patients in ~~385~~ 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, ~~and~~ Crohn's disease and ulcerative colitis clinical studies, representing ~~10,935~~11,561 patient-years of exposure in ~~5,884~~6,709 patients, the median follow-up was 1.0 years; ~~3.2~~1.1 years for ~~psoriasis~~ psoriatic disease studies, ~~1.0 year for psoriatic arthritis studies and~~ 0.6 year for Crohn's disease studies and 1.0 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in ~~58~~ 62 patients in ~~10,935~~11,561 patient-years of follow-up (incidence of 0.~~53~~ 54 per 100 patient-years of follow-up for ustekinumab-treated patients). The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.~~87~~ 93 [95% confidence interval: 0.~~66~~71, 1.~~14~~20], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, ~~melanoma,~~ colorectal, melanoma and breast cancers. The incidence of non-melanoma skin cancer was 0.49 per 100 patient-years of follow-up for ustekinumab-treated patients (~~53~~ 56 patients in ~~10,919~~11,545 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (~~4~~3:1) is comparable with the ratio expected in the general population (see section 4.4).

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, ~~and~~ Crohn's disease and ulcerative colitis.

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By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, ~~and~~ Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

In patients with Crohn's disease and ulcerative colitis, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and fecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase.

Immunisation
During the long term extension of Psoriasis Study 2 (PHOENIX 2), adult patients treated with STELARA for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of adult patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titers were similar among STELARA-treated and control patients.

Clinical efficacy

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Crohn's Disease
The safety and efficacy of ustekinumab was assessed in three randomized, double-blind, placebo-controlled, multicenter studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of ≥ 220 and ≤ 450). The clinical development program consisted of two 8-week intravenous induction studies (UNITI-1 and UNITI-2) followed by a 44 week subcutaneous randomized withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

The induction studies included 1409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analyzed through week 8 for both studies. Concomitant doses of oral corticosteroids, immunomodulators, aminosalicylates and antibiotics were permitted and 75% of patients continued to receive at least one of these medications. In both studies, patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion SmPC), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Patients in UNITI-1 had failed or were intolerant to prior anti-TNFα therapy. Approximately 48% of the patients had failed 1 prior anti-TNFα therapy and 52% had failed 2 or 3 prior anti-TNFα therapies. In this study, 29.1% of the patients had an inadequate initial response (primary non-responders), 69.4% responded but lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy, including corticosteroids or immunomodulators, and were either anti-TNF-α naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%).

In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 8). Clinical response and remission were significant as early as week 3 in ustekinumab treated patients and continued to improve through week 8. In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended intravenous induction dose.

Table 8: Induction of Clinical Response and Remission in UNITI-1 and UNITI 2

	UNITI-1*		**UNITI-2****	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of ustekinumab N = 209**
Clinical Remission, week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]

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Clinical Response (100 point), week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission
70 point response is defined as reduction in CDAI score by at least 70 points
* Anti-TNFα failures
** Conventional therapy failures
[a] $p < 0.001$
[b] $p < 0.01$

The maintenance study (IM-UNITI), evaluated 388 patients who achieved 100 point clinical response at week 8 of induction with ustekinumab in studies UNITI-1 and UNITI-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2).

Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups compared to the placebo group at week 44 (see Table 9).

Table 9: Maintenance of Clinical Response and Remission in IM-UNITI (week 44; 52 weeks from initiation of the induction dose)

	Placebo* **N = 131†**	**90 mg ustekinumab every 8 weeks** **N = 128†**	**90 mg ustekinumab every 12 weeks** **N = 129†**
Clinical Remission	36%	53%[a]	49%[b]
Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who entered from study CRD3002‡	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)[c]	57% (30/53)
who entered from study CRD3001§	26% (16/61)	41% (23/56)	39% (22/57)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission
* The placebo group consisted of patients who were in response to ustekinumab and were randomized to receive placebo at the start of maintenance therapy.
† Patients who were in 100 point clinical response to ustekinumab at start of maintenance therapy
‡ Patients who failed conventional therapy but not anti-TNFα therapy
§ Patients who are anti-TNFα refractory/intolerant
[a] $p < 0.01$
[b] $p < 0.05$
[c] nominally significant ($p < 0.05$)

In IM-UNITI, 29 of 129 patients did not maintain response to ustekinumab when treated every 12 weeks and were allowed to dose adjust to receive ustekinumab every 8 weeks. Loss of response was defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dose adjustment.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNITI-1 and UNITI-2 induction studies (476 patients) entered into the non-randomized portion of the maintenance study (IM-UNITI) and received a 90 mg subcutaneous injection of ustekinumab at that time. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority maintained

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response (68.1%) and achieved remission (50.2%) at week 44, at proportions that were similar to the patients who initially responded to ustekinumab induction.

Of 131 patients who responded to ustekinumab induction, and were randomized to the placebo group at the start of the maintenance study, 51 subsequently lost response and received 90 mg ustekinumab subcutaneously every 8 weeks. The majority of patients who lost response and resumed ustekinumab did so within 24 weeks of the induction infusion. Of these 51 patients, 70.6% achieved clinical response and 39.2% percent achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among patients who entered the study extension, clinical remission and response were generally maintained through week 92 for both patients who failed TNF-therapies and those who failed conventional therapies.

No new safety concerns were identified in this study extension with up to 2 years of treatment in patients with Crohn's Disease.

Endoscopy
Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a substudy. The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p = 0.012).

Fistula Response
In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared to 5/11 (45.5%) exposed to placebo.

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo. Improvement in health-related quality of life was generally maintained during the extension through week 92.

Ulcerative colitis
The safety and efficacy of ustekinumab was assessed in two randomized, double-blind, placebo-controlled, multicenter studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2). The clinical development program consisted of one intravenous induction study (referred to as UNIFI-I) with treatment of up to 16 weeks followed by a 44 week subcutaneous randomized withdrawal maintenance study (referred to as UNIFI-M) representing at least 52 weeks of therapy.

Efficacy results presented for UNIFI-I and UNIFI-M were based on central review of endoscopies.

UNIFI-I included 961 patients. The primary endpoint for the induction study was the proportion of subjects in clinical remission at week 8. Patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1, section 4.2), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

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Concomitant doses of oral corticosteroids, immunomodulators, and aminosalicylates were permitted and 90% of patients continued to receive at least one of these medications. Enrolled patients had to have failed conventional therapy (corticosteroids or immunomodulators) or at least one biologic (a TNFα antagonist and/or vedolizumab). 49% of patients had failed conventional therapy, but not a biologic (of which 94% where biological-naïve). 51% of patients had failed or were intolerant to a biologic. Approximately 50% of the patients had failed at least 1 prior anti-TNFα therapy (of which 48% were primary non-responders) and 17% had failed at least 1 anti-TNFα therapy and vedolizumab.

In UNIFI-I a significantly greater proportion of patients were in clinical remission in the ustekinumab treated group compared to placebo at week 8 (Table 10). As early as Week 2, the earliest scheduled study visit, and at each visit thereafter, a higher proportion of ustekinumab patients had no rectal bleeding or achieved normal stool frequency as compared with placebo patients. Significant differences in partial Mayo score and symptomatic remission were observed between ustekinumab and placebo as early as Week 2.

Efficacy was higher in the tiered dose group (6 mg/kg) compared to the 130 mg dose group in select endpoints, and tiered dosing is therefore the recommended intravenous induction dose.

Table 10: Summary of Key Efficacy Outcomes in UNIFI-I (Week 8)

	Placebo N = 319	**Recommended dose of ustekinumab£ N =322**
Clinical Remission*	5%	16%[a]
In patients who failed conventional therapy, but not a biologic	9% (15/158)	19% (29/156)[c]
In patients who failed biological therapy¥	1% (2/161)	13% (21/166)[b]
In patients who failed both a TNF and vedolizumab	0% (0/47)	10% (6/58%)[c]
Clinical Response§	31%	62%[a]
In patients who failed conventional therapy, but not a biologic	35% (56/158)	67% (104/156)[b]
In patients who failed biological therapy¥	27% (44/161)	57% (95/166)[b]
In patients who failed both a TNF and vedolizumab	28% (13/47)	52% (30/58)[c]
Mucosal Healing†	14%	27%[a]
In patients who failed conventional therapy, but not a biologic	21% (33/158)	33% (52/156)[c]
In patients who failed biological therapy	7% (11/161)	21% (35/166)[b]
Symptomatic Remission‡	23%	45%[b]
Combined Symptomatic Remission and Mucosal Healing⊥	8%	21%[b]

£ Infusion dose of ustekinumab using the weight-based dosage regimen specified in *Table 1*.
* Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.
§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
¥ A TNFα antagonist and/or vedolizumab.
† Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1.
‡ Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
⊥ Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
[a] $p < 0.001$
[b] Nominally significant ($p < 0.001$)
[c] Nominally significant ($p < 0.05$)

UNIFI-M, evaluated 523 patients who achieved clinical response with single IV administration of ustekinumab in UNIFI-I. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the STELARA Solution for injection (vial) and Solution for injection in pre filled syringe SmPC).

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Significantly greater proportions of patients were in clinical remission in both ustekinumab treated groups compared to the placebo group at week 44 (see Table 11).

Table 11: Summary of Key Efficacy Measures in UNIFI-M (week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 175	**90 mg ustekinumab every 8 Weeks** N = 176	**90 mg ustekinumab every 12 Weeks** N = 172
Clinical Remission**	24%	44% [a]	38% [b]
In patients who failed conventional therapy, but not a biologic	31% (27/87)	48% (41/85)[d]	49% (50/102) [d]
In patients who failed biological therapy[¥]	17% (15/88)	40% (36/91) [c]	23% (16/70) [d]
In patients who failed both a TNF and vedolizumab	15% (4/27)	33% (7/21)[e]	23% (5/22)[e]
Maintenance of Clinical Response through week 44[§]	45%	71% [a]	68% [a]
In patients who failed conventional therapy, but not a biologic	51% (44/87)	78% (66/85) [c]	77% (78/102) [c]
In patients who failed biological therapy[¥]	39% (34/88)	65% (59/91) [c]	56% (39/70) [d]
In patients who failed both a TNF and vedolizumab	41% (11/27)	67% (14/21)[e]	50% (11/22)[e]
Mucosal Healing[†]	29%	51% [a]	44% [b]
Maintenance of Clinical Remission through week 44[£]	38% (17/45)	58% (22/38)	65% (26/40) [c]
Corticosteroid Free Clinical Remission[€]	23%	42% [a]	38% [b]
Durable Remission[I]	35%	57% [c]	48% [d]
Symptomatic Remission[‡]	45%	68% [c]	62% [d]
Combined Symptomatic Remission and Mucosal Healing[ɟ]	28%	48% [c]	41% [d]

* Following response to IV ustekinumab.
** Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.
§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
¥ A TNFα antagonist and/or vedolizumab.
† Mucosal healing is defined as a Mayo endoscopic sub-score of 0 or 1.
£ Maintenance of clinical remission through Week 44 is defined as patients in clinical remission through Week 44 among patients in clinical remission at maintenance baseline.
€ Corticosteroid-free clinical remission is defined as patients in clinical remission and not receiving corticosteroids at Week 44.
I Durable Remission is defined as partial Mayo remission at ≥80% of all visits prior to Week 44 and in partial Mayo remission at last visit (Week 44).
‡ Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
ɟ Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
[a] $p < 0.001$
[b] $p < 0.05$
[c] Nominally significant ($p < 0.001$)
[d] Nominally significant ($p < 0.05$)
[e] Not statistically significant

The beneficial effect of ustekinumab on clinical response, mucosal healing and clinical remission was observed in induction and in maintenance both in patients who failed conventional therapy but not a biologic therapy, as well as in those who had failed at least one prior TNFα antagonist therapy including in patients with a primary non-response to TNFα antagonist therapy. A beneficial effect was also observed in induction in patients who failed at least one prior TNFα antagonist therapy and vedolizumab, however the number of patients in this subgroup was too small to draw definitive conclusions about the beneficial effect in this group during maintenance.

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Week 16 Responders to Ustekinumab Induction
Ustekinumab treated patients who were not in response at week 8 of UNIFI-I received an administration of 90 mg SC ustekinumab at week 8 (36% of patients). Of those patients, 9% of patients who were initially randomized to the recommended induction dose achieved clinical remission and 58% achieved clinical response at Week 16.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNFI-I study but were in response at week 16 (157 patients) entered into the non-randomized portion of UNIFI-M and continued to receive maintenance dosing every 8 weeks; among these patients, a majority (62%) maintained response and 30% achieved remission at week 44.

Endoscopic Normalization
Endoscopic normalization was defined as a Mayo endoscopic subscore of 0 and was observed as early as week 8 of UNIFI-I. At week 44 of UNIFI-M, it was achieved in 24% and 29% of patients treated with ustekinumab every 12 or 8 weeks, respectively, as compared to 18% of patients in the placebo group.

Histologic & Histo-Endoscopic Mucosal Healing
Histologic healing (defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) was assessed at week 8 of UNIFI-I and Week 44 of UNIFI-M. At week 8, after a single intravenous induction dose, significantly greater proportions of patients in the recommended dose group achieved histologic healing (36%) compared with patients in the placebo group (22%). At Week 44 maintenance of this effect was observed with significantly more patients in histologic healing in the every 12 week (54%) and every 8 week (59%) ustekinumab groups as compared to placebo (33%).

A combined endpoint of histo-endoscopic mucosal healing defined as subjects having both mucosal healing and histologic healing was evaluated at week 8 of UNIFI-I and week 44 of UNIFI-M. Patients receiving ustekinumab at the recommended dose showed significant improvements on the histo-endoscopic mucosal healing endpoint at week 8 in the ustekinumab group (18%) as compared to the placebo group (9%). At week 44, maintenance of this effect was observed with significantly more patients in histo-endoscopic mucosal healing in the every 12 week (39%) and every 8 week (46%) ustekinumab groups as compared to placebo (24%).

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), SF-36 and EuroQoL-5D (EQ-5D) questionnaires.

At week 8 of UNIFI-I, patients receiving ustekinumab showed significantly greater and clinically meaningful improvements on IBDQ total score, EQ-5D and EQ-5D VAS, and SF-36 Mental Component Summary Score and SF-36 Physical Component Summary Score when compared to placebo. These improvements were maintained in ustekinumab-treated patients in UNIFI-M through week 44.

Patients receiving ustekinumab experienced significantly more improvements in work productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI-GH questionnaire than patients receiving placebo.

Hospitalizations and ulcerative colitis (UC) related surgeries
Through week 8 of UNIFI-I, the proportions of subjects with UC disease related hospitalizations were significantly lower for subjects in the ustekinumab recommended dose group (1.6%, 5/322) compared with subjects in the placebo group (4.4%, 14/319) and no subjects underwent UC disease related surgeries in subjects receiving ustekinumab at the recommended induction dose compared to 0.6% (2/319) subjects in the placebo group.

Through week 44 of UNIFI-M, a significantly lower number of UC-related hospitalizations was observed in subjects in the combined ustekinumab group (2.0%, 7/348) as compared with subjects in the placebo group (5.7%, 10/175). A numerically lower number of subjects in the ustekinumab group (0.6%,

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2/348) underwent UC disease related surgeries compared with subjects in the placebo group (1.7%, 3/175) through week 44.

Immunogenicity
Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with both increased clearance and reduced efficacy of ustekinumab, except in patients with Crohn's disease or ulcerative colitis where no reduced efficacy was observed. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in Crohn's Disease and ulcerative colitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
The median time to reach the maximum serum concentration (t_{max}) was 8.5 days after a single 90 mg subcutaneous administration in healthy subjects. The median t_{max} values of ustekinumab following a single subcutaneous administration of either 45 mg or 90 mg in patients with psoriasis were comparable to those observed in healthy subjects.

The absolute bioavailability of ustekinumab following a single subcutaneous administration was estimated to be 57.2% in patients with psoriasis.

Distribution
Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Biotransformation
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with psoriasis, psoriatic arthritis, ~~or~~ Crohn's disease~~,~~ or ulcerative colitis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies. In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 l/day and 15.7 l, respectively, in patients with psoriasis. The CL/F of ustekinumab was not impacted by gender. Population pharmacokinetic analysis showed that there was a trend towards a higher clearance of ustekinumab in patients who tested positive for antibodies to ustekinumab.

Dose linearity
The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg or following a single subcutaneous administration at doses ranging from approximately 24 mg to 240 mg in patients with psoriasis.

Single dose versus multiple doses
Serum concentration-time profiles of ustekinumab were generally predictable after single or multiple subcutaneous dose administrations. In patients with psoriasis, steady-state serum concentrations of ustekinumab were achieved by week 28 after initial subcutaneous doses at Weeks 0 and 4 followed by doses every 12 weeks. The median steady-state trough concentration ranged from 0.21 µg/mL to 0.26 µg/mL (45 mg) and from 0.47 µg/mL to 0.49 µg/mL (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

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In patients with Crohn's disease and ulcerative colitis, following an intravenous dose of ~6 mg/kg, starting at week 8, subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. In patients with Crohn's disease, median steady-state trough concentrations ranged from 1.97 µg/mL to 2.24 µg/mL and from 0.61 µg/mL to 0.76 µg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks respectively. In patients with ulcerative colitis, median steady-state trough concentrations ranged from 2.69 µg/mL to 3.09 µg/mL and from 0.92 µg/mL to 1.19 µg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks. The steady-state trough ustekinumab levels resulting from 90 mg ustekinumab every 8 weeks were associated with higher clinical remission rates as compared to the steady-state trough levels following 90 mg every 12 weeks.

Impact of weight on pharmacokinetics
In a population pharmacokinetic analysis using data from patients with psoriasis, body weight was found to be the most significant covariate affecting the clearance of ustekinumab. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared to patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared to patients with weight ≤ 100 kg. The median trough serum concentrations of ustekinumab in patients with higher weight (> 100 kg) in the 90 mg group were comparable to those in patients with lower weight (≤ 100 kg) in the 45 mg group. Similar results were obtained from a confirmatory population pharmacokinetic analysis using data from patients with psoriatic arthritis.

Dosing frequency adjustment
In patients with Crohn's disease and ulcerative colitis, based on observed data and population PK analyses, randomized subjects who lost response to treatment had lower serum ustekinumab concentrations over time compared with subjects who did not lose response. In Crohn's disease, dose adjustment from 90 mg every 12 weeks to 90 mg every 8 weeks was associated with an increase in trough serum ustekinumab concentrations and an accompanying increase in efficacy. In ulcerative colitis, population PK model based simulations demonstrated that adjusting dosing from 90 mg every 12 weeks to every 8 weeks would be expected to result in a 3-fold increase in steady-state trough ustekinumab concentrations. Additionally on the basis of clinical trial data in patients with ulcerative colitis, a positive exposure-response relationship was established between trough concentrations, and clinical remission and mucosal healing.

Special populations
No pharmacokinetic data are available in patients with impaired renal or hepatic function.
No specific studies have been conducted in elderly patients.

The pharmacokinetics of ustekinumab were generally comparable between Asian and non-Asian patients with psoriasis and ulcerative colitis.

In patients with Crohn's disease and ulcerative colitis, variability in ustekinumab ~~CL~~ clearance was affected by body weight, serum albumin level, ~~CRP, TNF antagonist failure status,~~ sex, ~~race (Asian versus non-Asian),~~ and antibody to ustekinumab status while body weight was the main covariate affecting the volume of distribution. ~~Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.~~ Additionally in Crohn's disease, clearance was affected by C-reactive protein, TNF antagonist failure status and race (Asian versus non-Asian). ~~The impact of these statistically significant covariates on the respective PK parameters was within ± 20% when evaluated across a representative range of covariate values or categories in the data which is within the overall variability observed in the PK of ustekinumab.~~ The impact of these covariates was within ± 20% of the typical or reference value of the respective PK parameter, thus dose adjustment is not warranted for these covariates. Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.

In the population pharmacokinetic analysis, there were no indications of an effect of tobacco or alcohol on the pharmacokinetics of ustekinumab.

Serum ustekinumab concentrations in paediatric psoriasis patients 12 to 17 years of age, treated with the recommended weight-based dose were generally comparable to those in the adult psoriasis population

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treated with the adult dose, while serum ustekinumab concentrations in paediatric psoriasis patients treated with half of the recommended weight-based dose were generally lower than those in adults.

Regulation of CYP450 enzymes
The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 4.5).

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6.6 Special precautions for disposal and other handling

The solution in the STELARA vial or pre-filled syringe should not be shaken. The solution should be visually inspected for particulate matter or discoloration prior to subcutaneous administration. The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for proteinaceous solutions. The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present. Before administration, STELARA should be allowed to reach room temperature (approximately half an hour). Detailed instructions for use are provided in the package leaflet.

STELARA does not contain preservatives; therefore any unused medicinal product remaining in the vial and the syringe should not be used. STELARA is supplied as a sterile, single-use vial or single-use pre-filled syringe. The syringe, needle and vial must never be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

When using the single-dose vial, a 1 mL syringe with a 27 gauge, ½ inch (13 mm) needle is recommended.

השינויים המהותיים בעלון לצרכן מופיעים בסעיפים הבאים:

1. למה מיועדת התרופה?

סטלרה מיועדת לטיפול :

סטלרה משמשת לטיפול במחלות הדלקתיות הבאות:

- במחלת פסוריאזיס – במבוגרים וילדים מגיל 12 ומעלה.
- בדלקת מפרקים ספחתית – במבוגרים.
- במחלת קרוהן בדרגת חומרה בינונית עד קשה – במבוגרים.
- בכוליטיס כיבית בדרגת חומרה בינונית עד קשה – במבוגרים.

פסוריאזיס

פסוריאזיס הוא מצב בעור אשר גורם לדלקת המשפיעה על העור והציפורניים. סטלרה מפחיתה את הדלקת ואת סימני המחלה האחרים.

סטלרה משמשת במבוגרים בפסוריאזיס בדרגת חומרה בינונית עד חמורה, שאינם יכולים לקבל טיפול בציקלוספורין, מתותרקסט או טיפול באור, או כאשר טיפולים אלה לא השפיעו.

סטלרה משמשת לטיפול בילדים ומתבגרים בני 12 ומעלה בפסוריאזיס בדרגת חומרה בינונית עד חמורה שאינם יכולים לסבול טיפול באור או טיפול מערכתי (סיסטמי) אחר או אם טיפולים אלה לא השפיעו.

דלקת מפרקים ספחתית

דלקת מפרקים ספחתית היא מחלה דלקתית של המפרקים, מלווה בדרך כלל בפסוריאזיס. אם הינך סובל מדלקת מפרקים ספחתית פעילה, תטופל תחילה בתרופות אחרות. אם לא תגיב באופן מספק לתרופות האחרות, ייתכן ותקבל סטלרה בכדי:

- להפחית את סימני ותסמיני מחלתך.

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- לשפר את תפקודך הפיזי.
- להאט את הנזק הנגרם למפרקים.

מחלת קרוהן

מחלת קרוהן הינה מחלה דלקתית של המעיים. אם הינך סובל ממחלת קרוהן, תטופל תחילה בתרופות אחרות. אם לא תגיב באופן מספק לתרופות אחרות או שלא תוכן לסבול אותן, ייתכן ותקבל סטלרה להפחתת סימני ותסמיני מחלתך.

כולטיס כיבית

כוליטיס כיבית הינה מחלה דלקתית של המעיים. אם הינך סובל מכוליטיס כיבית, תטופל תחילה בתרופות אחרות. אם לא תגיב באופן מספק לתרופות אחרות או שלא תוכן לסבול אותן, ייתכן ותקבל סטלרה להפחתת סימני ותסמיני מחלתך.

...

2. לפני השימוש בתרופה

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

...

ילדים ומתבגרים:

סטלרה אינה מיועדת לטיפול בפסוריאזיס בילדים מתחת לגיל 12 ובדלקת מפרקים ספחתית, ~~או~~ במחלת קרוהן או בכוליטיס כיבית בילדים מתחת לגיל 18 כיוון שלא נבדקה בקבוצת גילאים זו.

3. כיצד תשתמש בתרופה?

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המינון המקובל בדרך כלל הוא:

מבוגרים מעל גיל 18:

במחלת פסוריאזיס או בדלקת מפרקים ספחתית

- המנה ההתחלתית המומלצת היא 45 מ"ג סטלרה. חולים שמשקלם מעל 100 קילוגרם (ק"ג) עשויים להתחיל במנה של 90 מ"ג במקום 45 מ"ג.
- לאחר קבלת המנה ההתחלתית, תינתן המנה השנייה כעבור 4 שבועות ובהמשך כל 12 שבועות. המנות העוקבות הן בדרך כלל זהות למנה ההתחלתית.

במחלת קרוהן או כוליטיס כיבית

- במהלך הטיפול, המנה הראשונה כ- 6 מ"ג\ ק"ג ,תינתן לך ע"י על ידי הרופא המטפל באמצעות עירוי בוריד בזרוע (intravenous infusion). לאחר קבלת המנה ההתחלתית, תקבל את המנה הבאה של 90 מ"ג סטלרה בזריקה תת עורית (subcutaneously) אחרי 8 שבועות, וכל 12 שבועות לאחר מכן.
- לאחר קבלת הזריקה התת עורית הראשונה,חלק מהמטופלים ייתכן ויקבלו סטלרה 90 מ"ג כל 8 שבועות. הרופא שלך יחליט מתי עליך לקבל את הזריקה הבאה שלך.

...

4. **תופעות לוואי**

כמו בכל תרופה, השימוש בסטלרה עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן.

תופעות לוואי חמורות-חלק מהחולים עלולים לסבול מתופעות לוואי חמורות הדורשות טיפול דחוף.

(X) **תגובה אלרגית- ייתכן ודורשת טיפול דחוף. יש לדווח מיד לרופא או לפנות לחדר מיון לקבלת טיפול רפואי דחוף**

אם הבחנת בסימנים הבאים:

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תגובה אלרגית חמורה (אנפילקסיס) היא נדירה (rare) בחולים המטופלים בסטלרה (ועלולה להופיע ב- 1-10 משתמשים מתוך 10,000). הסימנים כוללים:

- קשיי נשימה או בליעה
- לחץ דם נמוך שעלול לגרום לסחרחורת או תחושת סחרור
- התנפחות של הפנים, השפתיים, הפה, או הגרון,
- סימנים נפוצים (common) של תגובה אלרגית כוללים פריחה בעור וחרלת (היכולים להופיע בעד 1-10 מתוך 100 משתמשים)

במקרים נדירים, תגובה אלרגית ריאתית או דלקת בריאות דווחה בחולים המטופלים בסטלרה. ספר לרופא מיד אם החלו להתפתח תסמינים כגון שיעול, קוצר נשימה וחום~~, עלולים להיות גם סימן לתגובה אלרגית בראות לסטלרה~~.

אם הינך חווה תגובה אלרגית חריפה, ייתכן והרופא יחליט כי אינך יכול להשתמש יותר בסטלרה.

...

תופעות לוואי נוספות:

תופעות לוואי שכיחות (common)

תופעות שמופיעות ב 1-10 משתמשים מתוך 100

- שלשולים
- בחילה
- הקאות
- עייפות
- סחרחורת
- כאב ראש
- גרד (pruritus)
- כאבי גב, כאבי ~~מפרקים~~ שרירים או כאבי ~~שרירים~~ מפרקים
- כאב גרון
- אדמומיות וכאב באזור מתן ההזרקה
- זיהום בסינוסים

...

העלון לרופא והעלון לצרכן נשלחו לפרסום במלואם למאגר התרופות שבאתר משרד הבריאות. כמו כן, ניתן לקבלם מודפסים בפניה אלינו לטלפון 09-9591111 .

בברכה,
צפריר כהן
רוקח ממונה